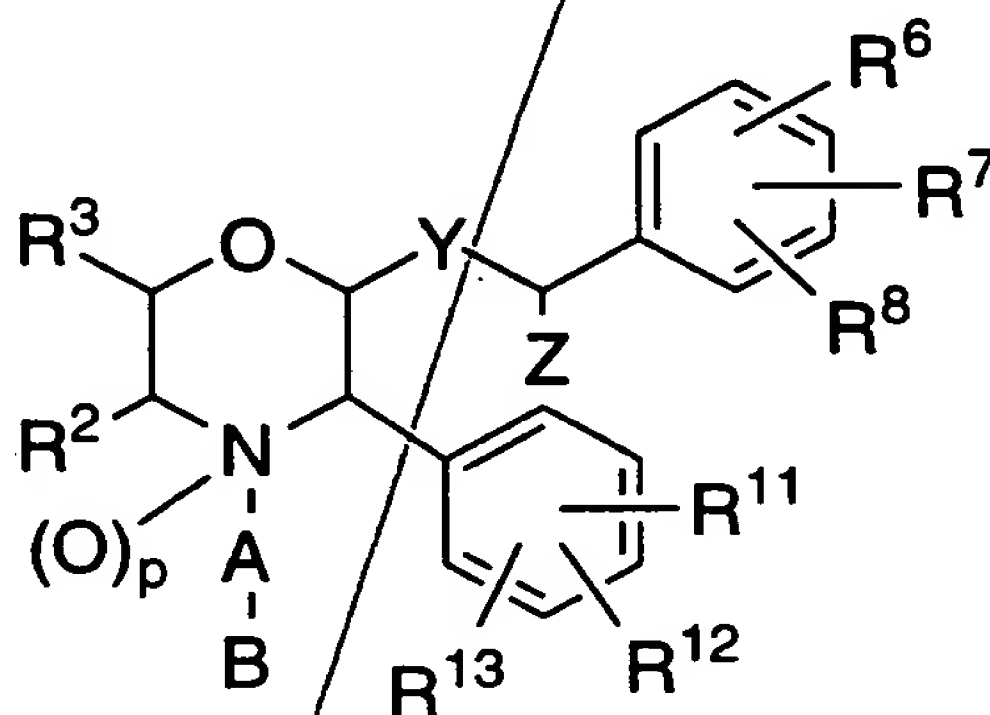


WHAT IS CLAIMED IS:

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Cl

1. A compound of structural formula:



5 or a pharmaceutically acceptable salt thereof, wherein:

R² and R³ are independently selected from the group consisting of:

- (1) hydrogen,
- (2) C₁-6 alkyl, unsubstituted or substituted with one or more of the substituents selected from:
 - (a) hydroxy,
 - (b) oxo,
 - (c) C₁-6 alkoxy,
 - (d) phenyl-C₁-3 alkoxy,
 - (e) phenyl,
 - (f) -CN,
 - (g) halo,
 - (h) -NR⁹R¹⁰, wherein R⁹ and R¹⁰ are independently selected from:
 - (i) hydrogen,
 - (ii) C₁-6 alkyl,
 - (iii) hydroxy-C₁-6 alkyl, and
 - (iv) phenyl,
 - (i) -NR⁹COR¹⁰, wherein R⁹ and R¹⁰ are as defined above,
 - (j) -NR⁹CO₂R¹⁰, wherein R⁹ and R¹⁰ are as

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- defined above,
- (k) $-\text{CONR}^9\text{R}^{10}$, wherein R^9 and R^{10} are as defined above,
- (l) $-\text{COR}^9$, wherein R^9 is as defined above, and
- 5 (m) $-\text{CO}_2\text{R}^9$, wherein R^9 is as defined above;
- (3) C2-6 alkenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:
- (a) hydroxy,
- 10 (b) oxo,
- (c) C1-6 alkoxy,
- (d) phenyl-C1-3 alkoxy,
- (e) phenyl,
- (f) $-\text{CN}$,
- 15 (g) halo,
- (h) $-\text{CONR}^9\text{R}^{10}$ wherein R^9 and R^{10} are as defined above,
- (i) $-\text{COR}^9$ wherein R^9 is as defined above,
- (j) $-\text{CO}_2\text{R}^9$, wherein R^9 is as defined above;
- 20 (4) C2-6 alkynyl;
- (5) phenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:
- (a) hydroxy,
- (b) C1-6 alkoxy,
- 25 (c) C1-6 alkyl,
- (d) C2-5 alkenyl,
- (e) halo,
- (f) $-\text{CN}$,
- (g) $-\text{NO}_2$,
- 30 (h) $-\text{CF}_3$,
- (i) $-(\text{CH}_2)_m-\text{NR}^9\text{R}^{10}$, wherein m , R^9 and R^{10} are as defined above,
- (j) $-\text{NR}^9\text{COR}^{10}$, wherein R^9 and R^{10} are as defined above,

- 5 (k) $-\text{NR}^9\text{CO}_2\text{R}^{10}$, wherein R^9 and R^{10} are as defined above,
(l) $-\text{CONR}^9\text{R}^{10}$, wherein R^9 and R^{10} are as defined above,
(m) $-\text{CO}_2\text{NR}^9\text{R}^{10}$, wherein R^9 and R^{10} are as defined above,
(n) $-\text{COR}^9$, wherein R^9 is as defined above;
(o) $-\text{CO}_2\text{R}^9$, wherein R^9 is as defined above;

10 and, alternatively, the groups R^2 and R^3 are joined together to form a carbocyclic ring selected from the group consisting of:

- (a) cyclopentyl,
(b) cyclohexyl,
(c) phenyl,

15 and wherein the carbocyclic ring is unsubstituted or substituted with one or more substituents selected from:

- (i) C₁-6alkyl,
(ii) C₁-6alkoxy,
20 (iii) $-\text{NR}^9\text{R}^{10}$, wherein R^9 and R^{10} are as defined above,
(iv) halo, and
(v) trifluoromethyl;

25 and, alternatively, the groups R^2 and R^3 are joined together to form a heterocyclic ring selected from the group consisting of:

- (a) pyrrolidinyl,
(b) piperidinyl,
(c) pyrrolyl,
(d) pyridinyl,
30 (e) imidazolyl,
(f) furanyl,
(g) oxazolyl,
(h) thienyl, and
(i) thiazolyl,

and wherein the heterocyclic ring is unsubstituted or substituted with one or more substituent(s) selected from:

- (i) C1-6alkyl,
- (ii) oxo,
- (iii) C1-6alkoxy,
- (iv) -NR⁹R¹⁰, wherein R⁹ and R¹⁰ are as defined above,
- (v) halo, and
- (vi) trifluoromethyl;

R⁶, R⁷ and R⁸ are independently selected from the group consisting of:

- (1) hydrogen;
- (2) C1-6 alkyl, unsubstituted or substituted with one or more of the substituents selected from:

- (a) hydroxy,
- (b) oxo,
- (c) C1-6 alkoxy,
- (d) phenyl-C1-3 alkoxy,
- (e) phenyl,
- (f) -CN,
- (g) halo,
- (h) -NR⁹R¹⁰, wherein R⁹ and R¹⁰ are as defined above,
- (i) -NR⁹COR¹⁰, wherein R⁹ and R¹⁰ are as defined above,
- (j) -NR⁹CO₂R¹⁰, wherein R⁹ and R¹⁰ are as defined above,
- (k) -CONR⁹R¹⁰, wherein R⁹ and R¹⁰ are as defined above,
- (l) -COR⁹, wherein R⁹ is as defined above, and
- (m) -CO₂R⁹, wherein R⁹ is as defined above;

- 5
- (3) C2-6 alkenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:
- (a) hydroxy,
 - (b) oxo,
 - (c) C1-6 alkoxy,
 - (d) phenyl-C1-3 alkoxy,
 - (e) phenyl,
 - (f) -CN,
 - (g) halo,
 - 10 (h) -CONR⁹R¹⁰ wherein R⁹ and R¹⁰ are as defined above,
 - (i) -COR⁹ wherein R⁹ is as defined above,
 - (j) -CO₂R⁹, wherein R⁹ is as defined above;
- 15
- (4) C2-6 alkynyl;
- (5) phenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:
- (a) hydroxy,
 - (b) C1-6 alkoxy,
 - (c) C1-6 alkyl,
 - 20 (d) C2-5 alkenyl,
 - (e) halo,
 - (f) -CN,
 - (g) -NO₂,
 - (h) -CF₃,
 - 25 (i) -(CH₂)_m-NR⁹R¹⁰, wherein m, R⁹ and R¹⁰ are as defined above,
 - (j) -NR⁹COR¹⁰, wherein R⁹ and R¹⁰ are as defined above,
 - (k) -NR⁹CO₂R¹⁰, wherein R⁹ and R¹⁰ are as defined above,
 - 30 (l) -CONR⁹R¹⁰, wherein R⁹ and R¹⁰ are as defined above,
 - (m) -CO₂NR⁹R¹⁰, wherein R⁹ and R¹⁰ are as defined above,

- (n) -COR⁹, wherein R⁹ is as defined above;
(o) -CO₂R⁹, wherein R⁹ is as defined above;
- (6) halo,
(7) -CN,
5 (8) -CF₃,
(9) -NO₂,
(10) -SR¹⁴, wherein R¹⁴ is hydrogen or C₁-5alkyl,
(11) -SOR¹⁴, wherein R¹⁴ is as defined above,
(12) -SO₂R¹⁴, wherein R¹⁴ is as defined above,
10 (13) NR⁹COR¹⁰, wherein R⁹ and R¹⁰ are as defined above,
(14) CONR⁹COR¹⁰, wherein R⁹ and R¹⁰ are as defined above,
(15) NR⁹R¹⁰, wherein R⁹ and R¹⁰ are as defined above,
(16) NR⁹CO₂R¹⁰, wherein R⁹ and R¹⁰ are as defined above,
15 (17) hydroxy,
(18) C₁-6alkoxy,
(19) COR⁹, wherein R⁹ is as defined above,
(20) CO₂R⁹, wherein R⁹ is as defined above,
20 (21) 2-pyridyl,
(22) 3-pyridyl,
(23) 4-pyridyl,
(24) 5-tetrazolyl,
(25) 2-oxazolyl, and
(26) 2-thiazolyl;

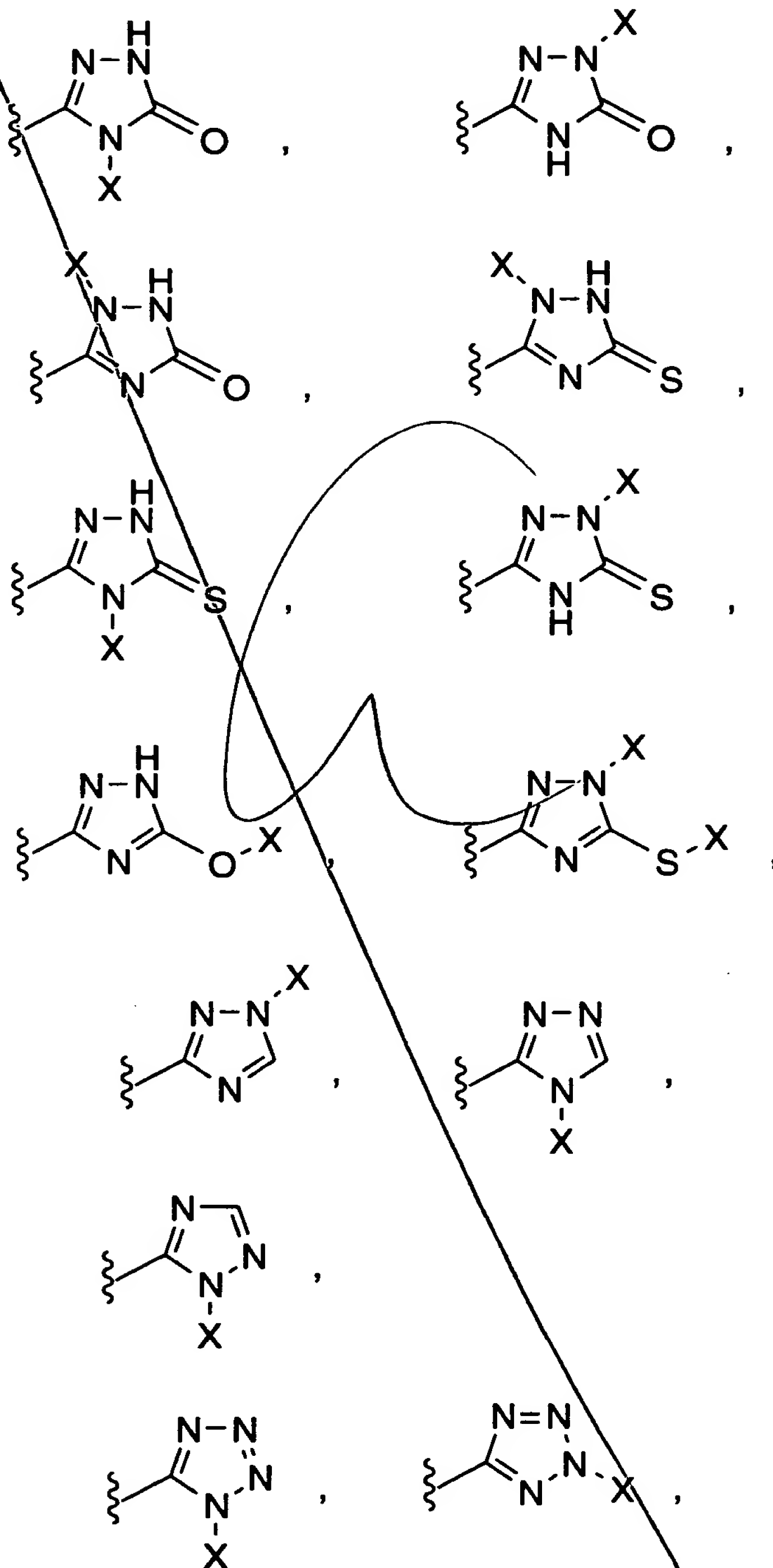
25 R¹¹, R¹² and R¹³ are independently selected from the definitions of R⁶, R⁷ and R⁸, or -OX;

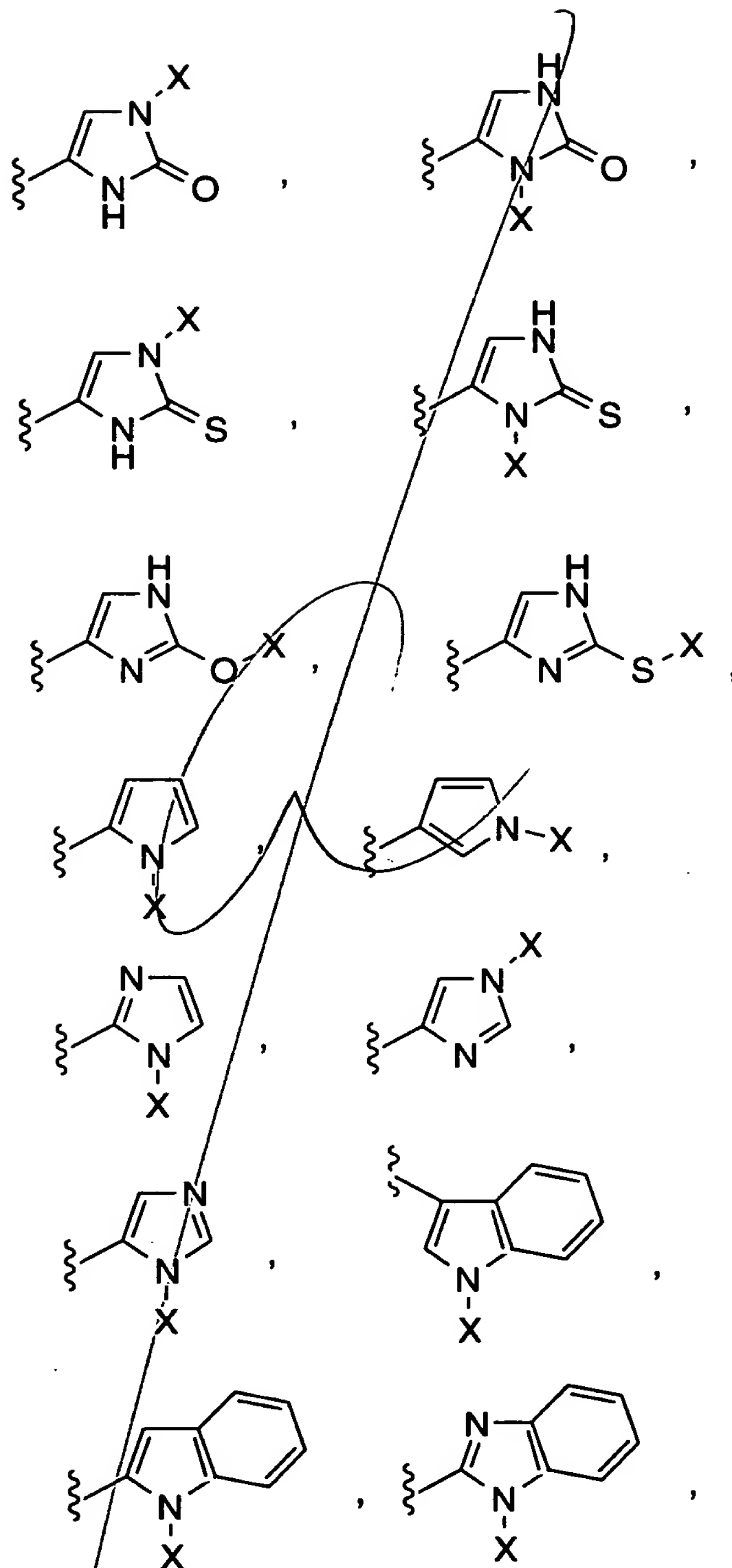
A is selected from the group consisting of:

- 30 (1) C₁-6 alkyl, unsubstituted or substituted with one or more of the substituents selected from:
(a) hydroxy,
(b) oxo,
(c) C₁-6 alkoxy,
(d) phenyl-C₁-3 alkoxy,

- 5
- (e) phenyl,
 - (f) -CN,
 - (g) halo, wherein halo is fluoro, chloro, bromo or iodo,
 - (h) -NR⁹R¹⁰, wherein R⁹ and R¹⁰ are as defined above,
 - (i) -NR⁹COR¹⁰, wherein R⁹ and R¹⁰ are as defined above,
 - (j) -NR⁹CO₂R¹⁰, wherein R⁹ and R¹⁰ are as defined above,
 - (k) -CONR⁹R¹⁰, wherein R⁹ and R¹⁰ are as defined above,
 - (l) -COR⁹, wherein R⁹ is as defined above, and
 - (m) -CO₂R⁹, wherein R⁹ is as defined above;
- 10
- (2) C₂-6 alkenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:
- 15
- (a) hydroxy,
 - (b) oxo,
 - (c) C₁-6 alkoxy,
 - (d) phenyl-C₁-3 alkoxy,
 - (e) phenyl,
 - (f) -CN,
 - (g) halo,
 - (h) -CONR⁹R¹⁰ wherein R⁹ and R¹⁰ are as defined above,
 - (i) -COR⁹ wherein R⁹ is as defined above, and
 - (j) -CO₂R⁹, wherein R⁹ is as defined above; and
- 20
- 25
- (3) C₂-6 alkynyl;

B is a heterocycle, wherein the heterocycle is selected from the group consisting of:





and wherein the heterocycle is substituted in addition to $-X$ with one or more substituent(s) selected from:

- (i) hydrogen;

- 5
- (ii) C1-6 alkyl, unsubstituted or substituted with halo, -CF₃, -OCH₃, or phenyl,
- (iii) C1-6 alkoxy,
- (iv) oxo,
- (v) hydroxy,
- (vi) thioxo,
- (vii) -SR⁹, wherein R⁹ is as defined above,
- (viii) halo,
- (ix) cyano,
- 10 (x) phenyl,
- (xi) trifluoromethyl,
- (xii) -(CH₂)_m-NR⁹R¹⁰, wherein m is 0, 1 or 2, and R⁹ and R¹⁰ are as defined above,
- (xiii) -NR⁹COR¹⁰, wherein R⁹ and R¹⁰ are
- 15 as defined above,
- (xiv) -CONR⁹R¹⁰, wherein R⁹ and R¹⁰ are as defined above,
- (xv) -CO₂R⁹, wherein R⁹ is as defined above, and
- 20 (xvi) -(CH₂)_m-OR⁹, wherein m and R⁹ are as defined above;

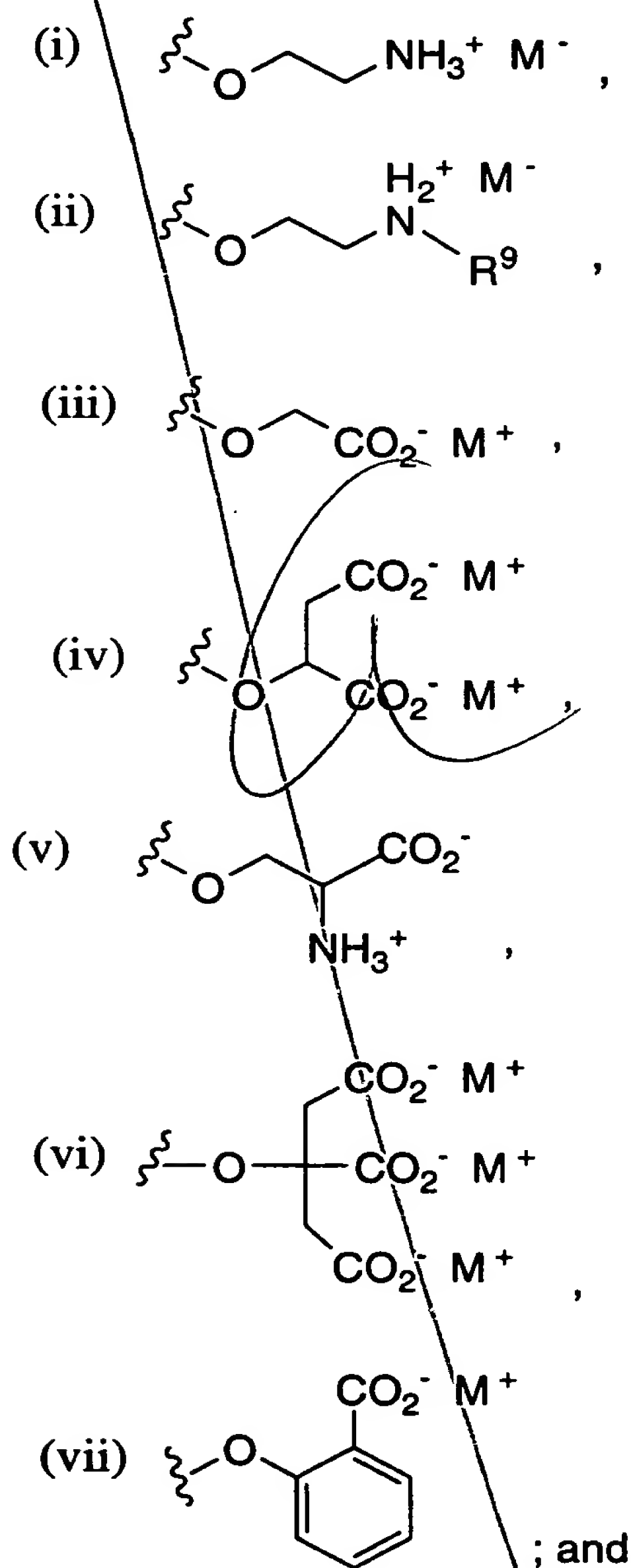
p is 0 or 1;

25 X is selected from:

- (a) -PO(OH)O⁻ • M⁺, wherein M⁺ is a pharmaceutically acceptable monovalent counterion,
- (b) -PO(O⁻)₂ • 2M⁺,
- (c) -PO(O⁻)₂ • D²⁺, wherein D²⁺ is a pharmaceutically
- 30 acceptable divalent counterion,
- (d) -CH(R⁴)-PO(OH)O⁻ • M⁺, wherein R⁴ is hydrogen or C1-3 alkyl,
- (e) -CH(R⁴)-PO(O⁻)₂ • 2M⁺,
- (f) -CH(R⁴)-PO(O⁻)₂ • D²⁺,

5

- (g) $-\text{SO}_3^- \cdot \text{M}^+$,
 (h) $-\text{CH}(\text{R}^4)-\text{SO}_3^- \cdot \text{M}^+$,
 (i) $-\text{CO}-\text{CH}_2\text{CH}_2-\text{CO}_2^- \cdot \text{M}^+$,
 (j) $-\text{CH}(\text{CH}_3)-\text{O}-\text{CO}-\text{R}^5$, wherein R^5 is selected from the group consisting of:



- (k) hydrogen, with the proviso that if p is 0 and none of R^{11} , R^{12} or R^{13} are $-\text{OX}$, then X is other than hydrogen;

Y is selected from the group consisting of:

- 5
- (1) a single bond,
 - (2) -O-,
 - (3) -S-,
 - (4) -CO-,
 - (5) -CH₂-,
 - (6) -CHR¹⁵-, and
 - (7) -CR¹⁵R¹⁶-, wherein R¹⁵ and R¹⁶ are independently
- 10 selected from the group consisting of:
- (a) C₁₋₆ alkyl, unsubstituted or substituted with one or more of the substituents selected from:
 - 15 (i) hydroxy,
 - (ii) oxo,
 - (iii) C₁₋₆ alkoxy,
 - (iv) phenyl-C₁₋₃ alkoxy,
 - (v) phenyl,
 - (vi) -CN,
 - (vii) halo,
 - 20 (viii) -NR⁹R¹⁰, wherein R⁹ and R¹⁰ are as defined above,
 - (ix) -NR⁹COR¹⁰, wherein R⁹ and R¹⁰ are as defined above,
 - (x) -NR⁹CO₂R¹⁰, wherein R⁹ and R¹⁰ are as defined above,
 - 25 (xi) -CONR⁹R¹⁰, wherein R⁹ and R¹⁰ are as defined above,
 - (xii) -COR⁹, wherein R⁹ is as defined above, and
 - (xiii) -CO₂R⁹, wherein R⁹ is as defined above;

(b) phenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:

- 5
- (i) hydroxy,
 - (ii) C1-6 alkoxy,
 - (iii) C1-6 alkyl,
 - (iv) C2-5 alkenyl,
 - (v) halo,
 - (vi) -CN,
 - (vii) -NO₂,
 - 10 (viii) -CF₃,
 - (ix) -(CH₂)_m-NR⁹R¹⁰, wherein m, R⁹ and R¹⁰ are as defined above,
 - (x) -NR⁹COR¹⁰, wherein R⁹ and R¹⁰ are as defined above,
 - 15 (xi) -NR⁹CO₂R¹⁰, wherein R⁹ and R¹⁰ are as defined above,
 - (xii) -CONR⁹R¹⁰, wherein R⁹ and R¹⁰ are as defined above,
 - (xiii) -CO₂NR⁹R¹⁰, wherein R⁹ and R¹⁰ are as defined above,
 - 20 (xiv) -COR⁹, wherein R⁹ is as defined above, and
 - (xv) -CO₂R⁹, wherein R⁹ is as defined above;

Z is selected from:

- 25
- (1) hydrogen,
 - (2) C1-6 alkyl, and
 - (3) hydroxy, with the proviso that if Y is -O-, Z is other than hydroxy, or if Y is -CHR¹⁵-, then Z and R¹⁵ are optionally joined together to form a double bond.

2. The compound of Claim 1 wherein:

R² and R³ are independently selected from the group consisting of:

- 5
- (1) hydrogen,
 - (2) C₁-6 alkyl,
 - (3) C₂-6 alkenyl, and
 - (4) phenyl;

R⁶, R⁷ and R⁸ are independently selected from the group consisting of:

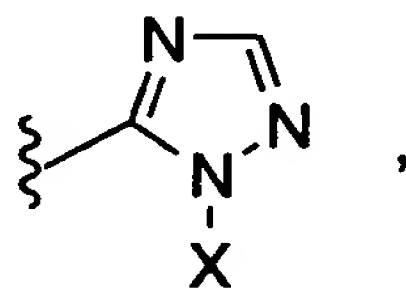
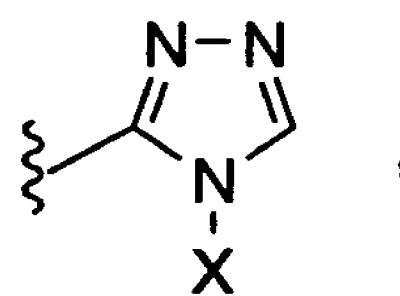
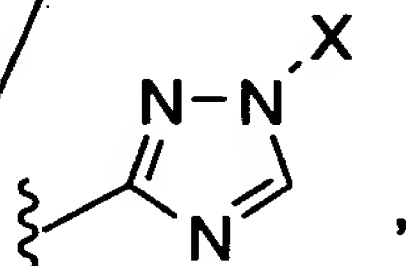
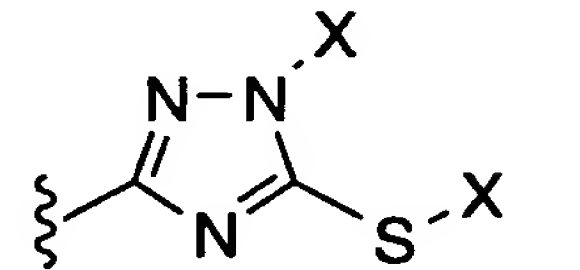
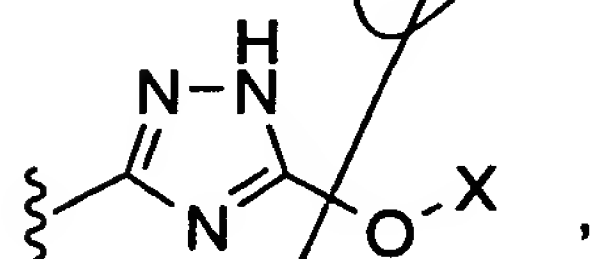
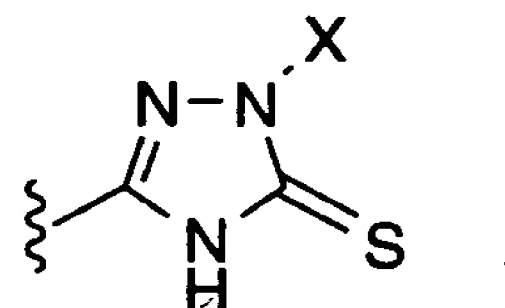
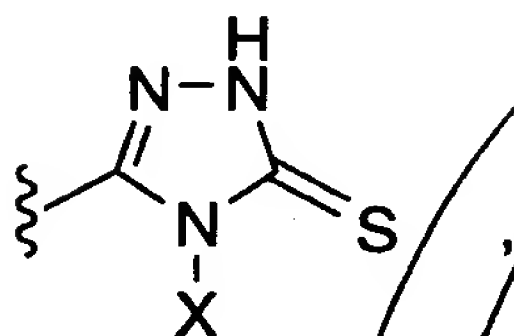
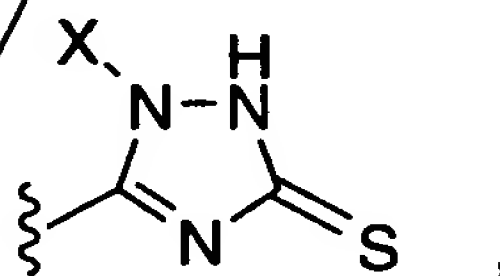
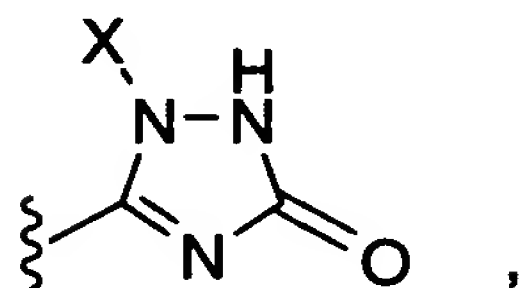
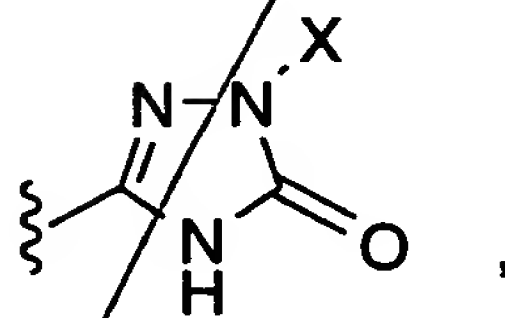
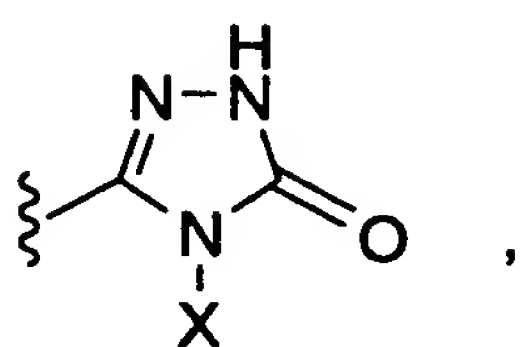
- 10
- (1) hydrogen,
 - (2) C₁-6 alkyl,
 - (3) fluoro,
 - (4) chloro,
 - (5) bromo,
 - 15 (6) iodo, and
 - (7) -CF₃;

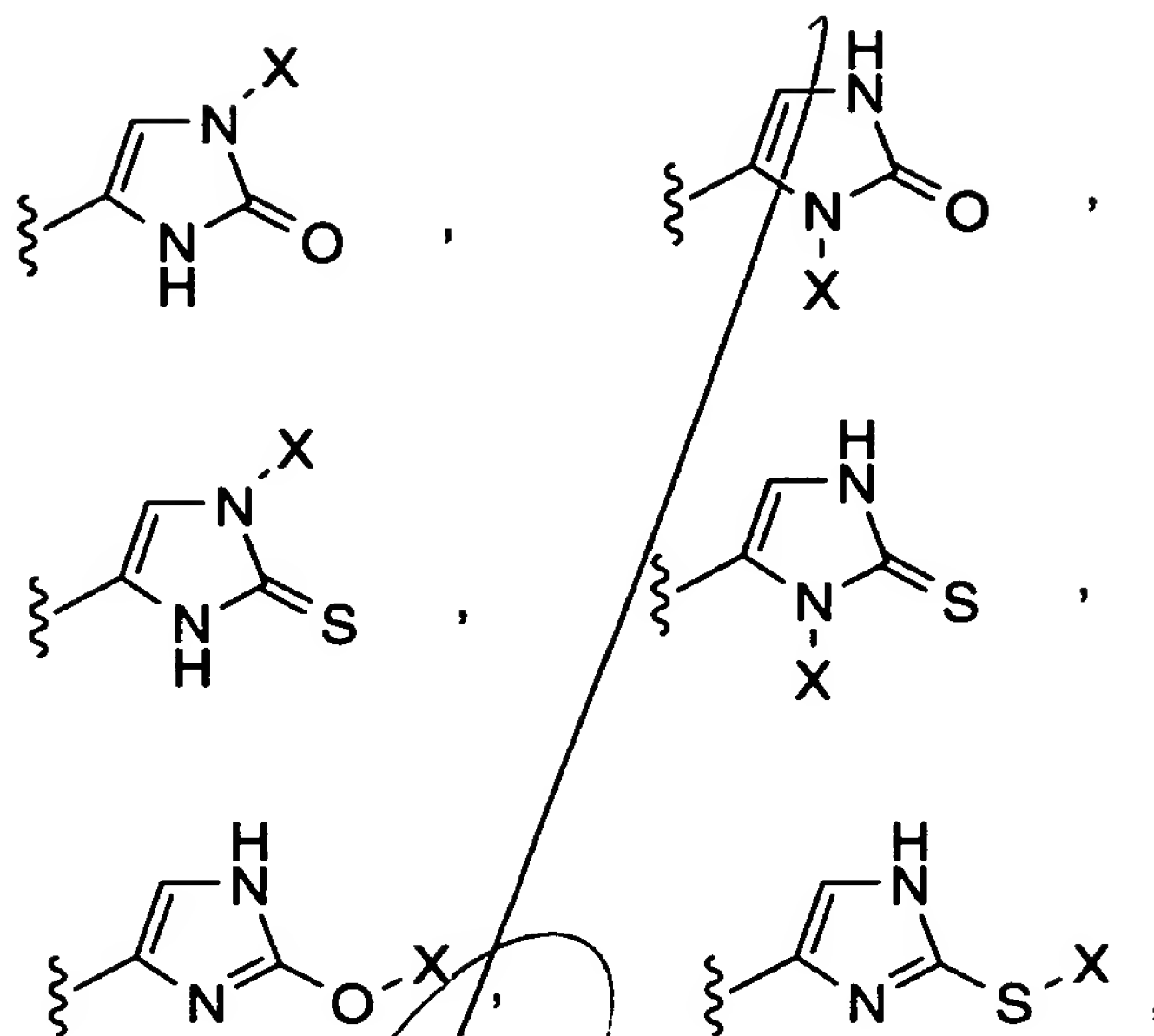
R¹¹, R¹² and R¹³ are independently selected from the group consisting of:

- 20
- (1) fluoro,
 - (2) chloro,
 - (3) bromo, and
 - (4) iodo;

25 A is unsubstituted C₁-6 alkyl;

B is selected from the group consisting of:



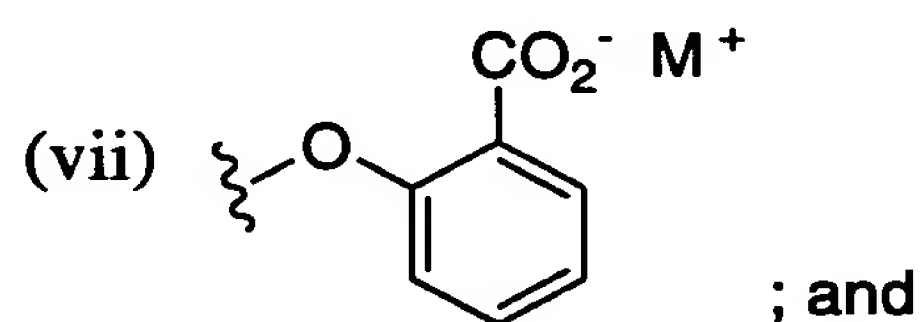
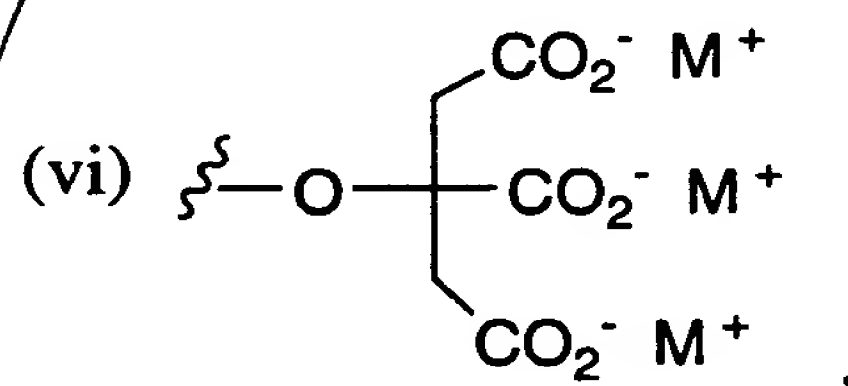
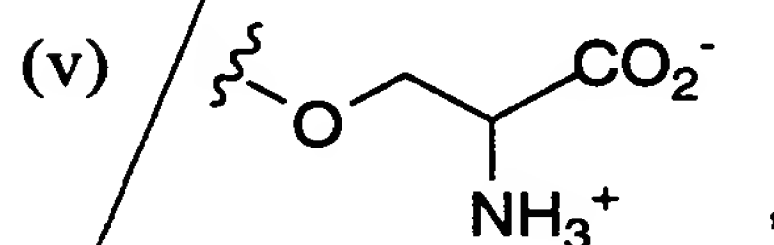
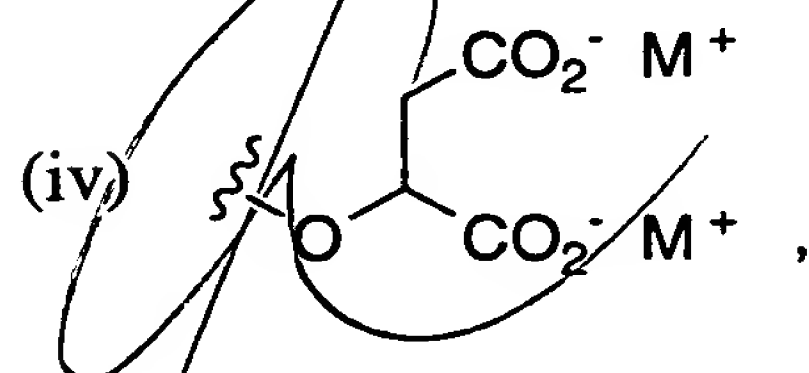
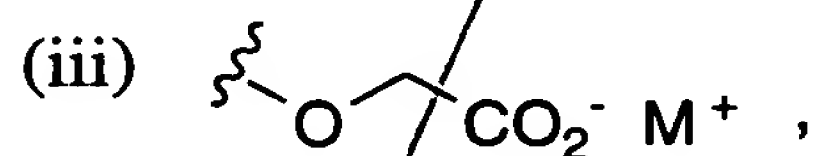
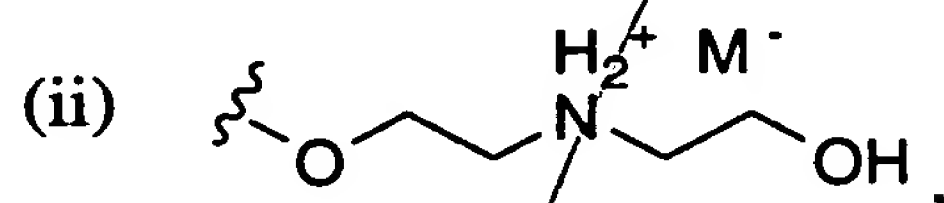
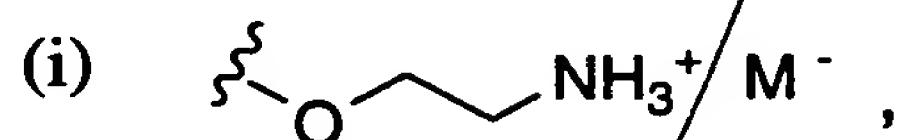


p is 0;

X is selected from:

- 5 (a) $-\text{PO}(\text{OH})\text{O}^- \cdot \text{M}^+$, wherein M^+ is a pharmaceutically acceptable monovalent counterion,
- (b) $-\text{PO}(\text{O}^-)_2 \cdot 2\text{M}^+$,
- (c) $-\text{PO}(\text{O}^-)_2 \cdot \text{D}^{2+}$, wherein D^{2+} is a pharmaceutically acceptable divalent counterion,
- 10 (d) $-\text{CH}(\text{R}^4)-\text{PO}(\text{OH})\text{O}^- \cdot \text{M}^+$, wherein R^4 is hydrogen or methyl,
- (e) $-\text{CH}(\text{R}^4)-\text{PO}(\text{O}^-)_2 \cdot 2\text{M}^+$, wherein R^4 is hydrogen or methyl,
- (f) $-\text{CH}(\text{R}^4)-\text{PO}(\text{O}^-)_2 \cdot \text{D}^{2+}$, wherein R^4 is hydrogen or methyl,
- 15 (i) $-\text{CO}-\text{CH}_2\text{CH}_2-\text{CO}_2^- \cdot \text{M}^+$,

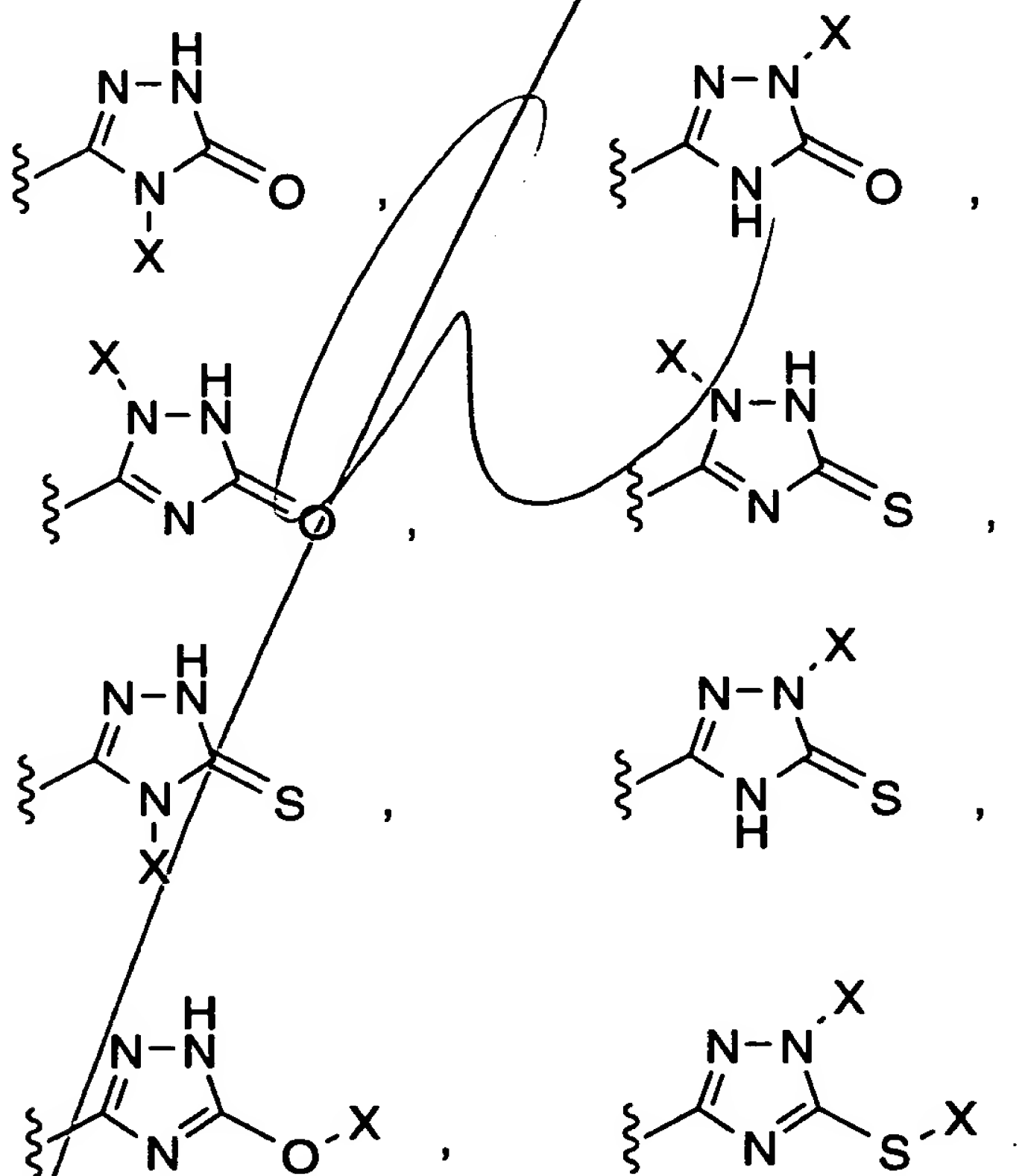
- (j) $-\text{CH}(\text{CH}_3)-\text{O}-\text{CO}-\text{R}^5$, wherein R^5 is selected from the group consisting of:

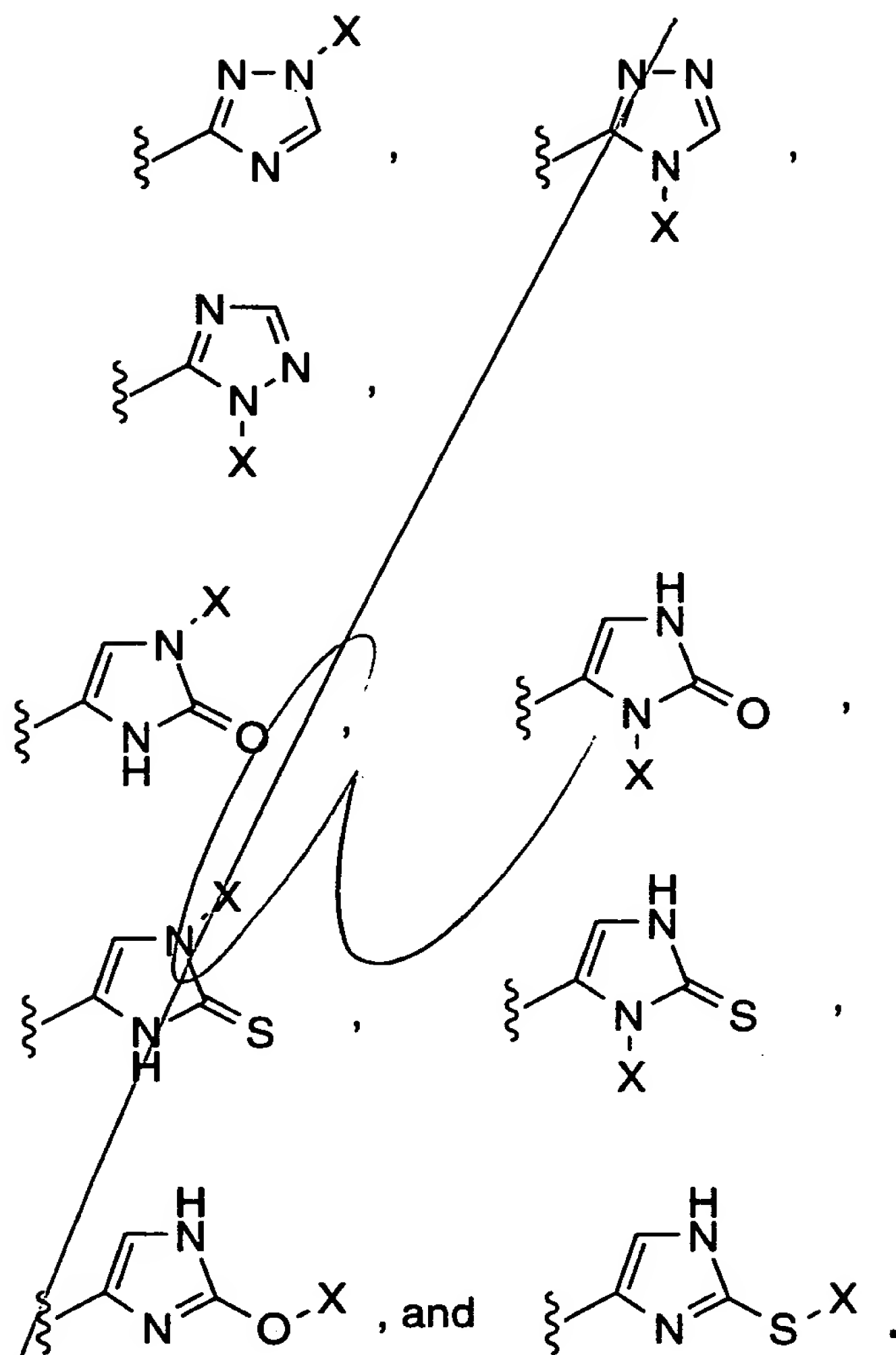


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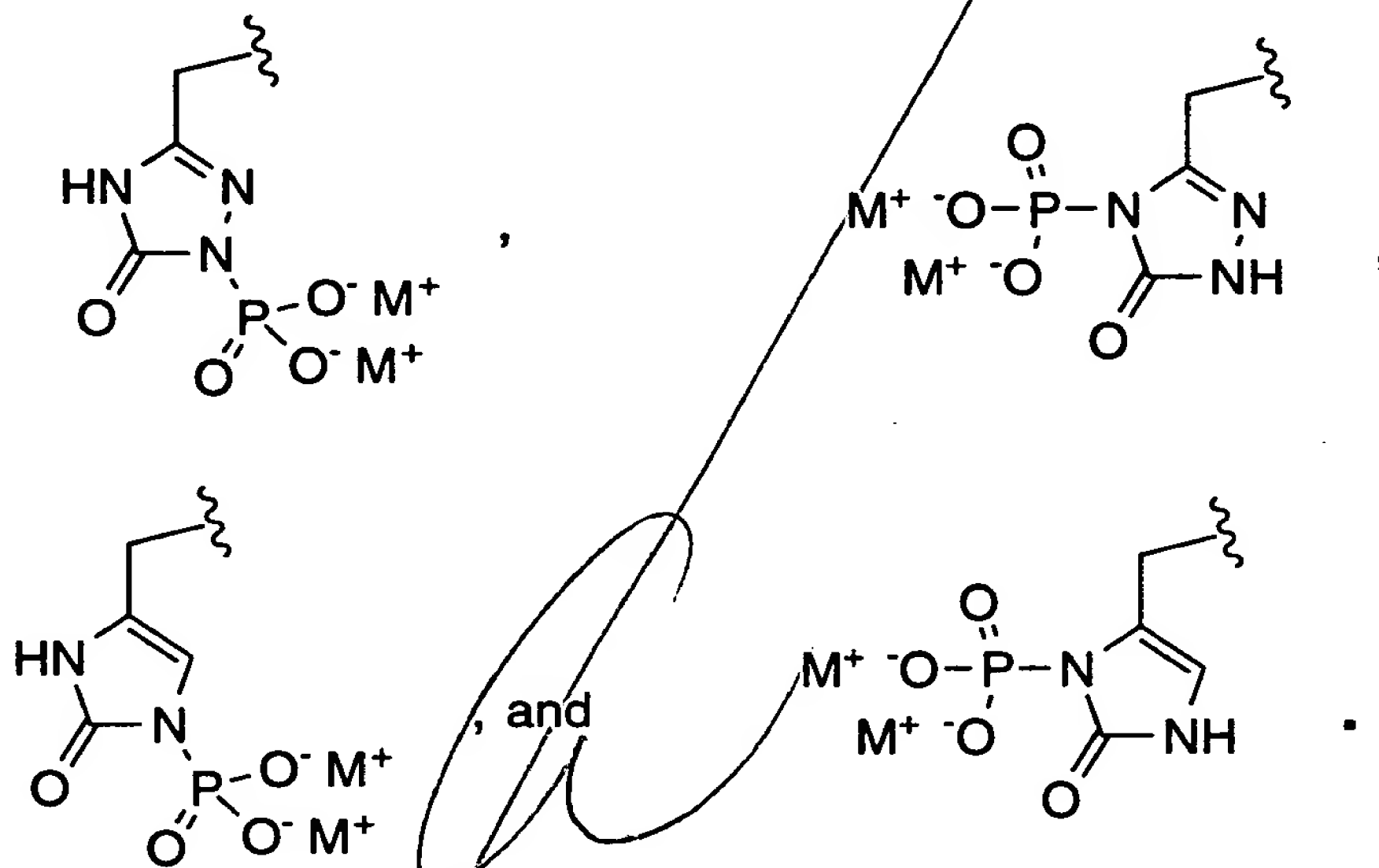
Y is -O-;
Z is hydrogen or C₁-4 alkyl.

3. The compound of Claim 1 wherein Z is C₁₋₄ alkyl.
4. The compound of Claim 1 wherein Z is -CH₃.
5. The compound of Claim 1 wherein A is -CH₂- or -CH(CH₃)-.
6. The compound of Claim 1 wherein -B is selected from the group consisting of:





7. The compound of Claim 1 wherein -A-B is selected from the group consisting of:



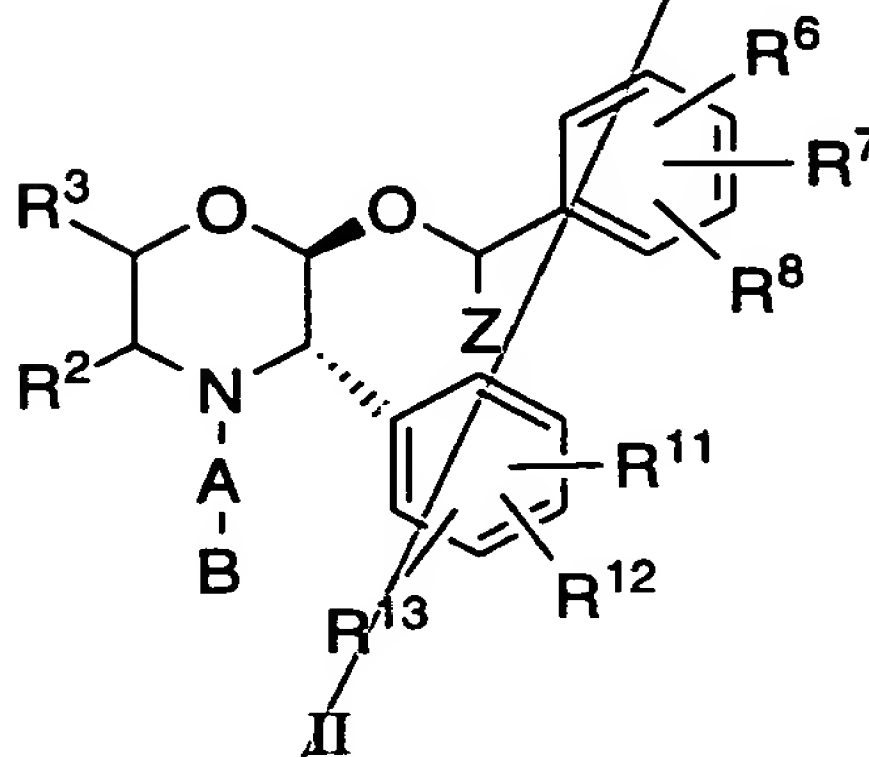
5

8. The compound of Claim 1 wherein X is selected from the group consisting of:

- (a) $\text{-PO(O}^-\text{)}_2 \cdot 2\text{M}^+$, wherein M^+ is a pharmaceutically acceptable monovalent counterion,
- (b) $\text{-PO(O}^-\text{)}_2 \cdot \text{D}^{2+}$, wherein D^{2+} is a pharmaceutically acceptable divalent counterion,
- (c) $\text{-CH(CH}_3\text{)-O-CO-CH}_2\text{CH}_2\text{-NH}_3^+ \cdot \text{M}^-$, and
- (d) $\text{-CH(CH}_3\text{)-O-CO-CH}_2\text{CH}_2\text{-NH}_2^+ \cdot (\text{CH}_2\text{CH}_2\text{-OH}) \cdot \text{M}^-$.

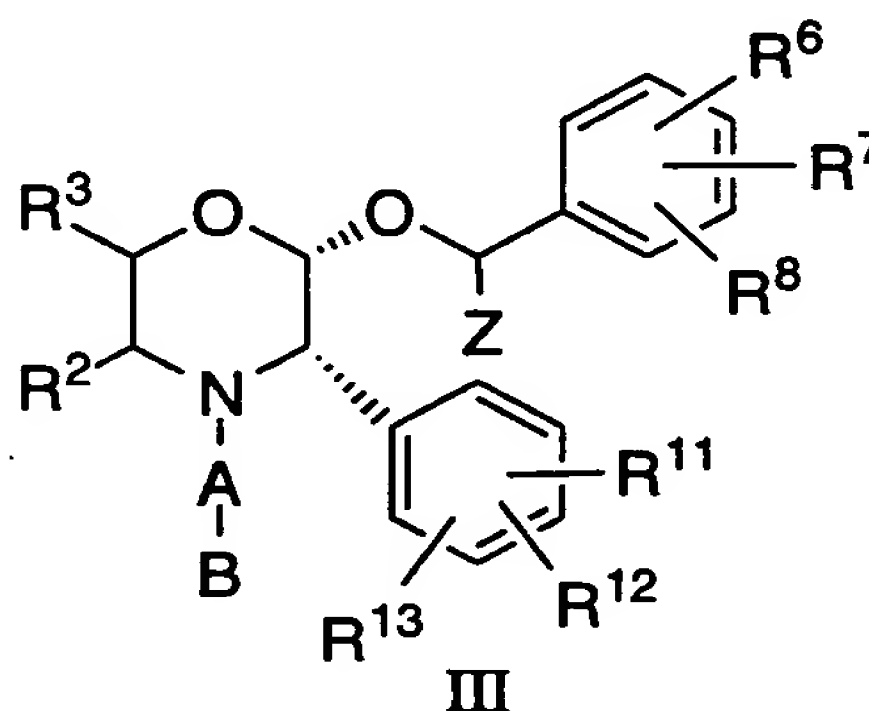
10

9. The compound of Claim 1 of the structural formula II:



5 or a pharmaceutically acceptable salt thereof, wherein R2, R3, R6, R7, R8, R11, R12, R13, A, B and Z are as defined in Claim 1.

10 10. The compound of Claim 1 of the structural formula III:



15 or a pharmaceutically acceptable salt thereof, wherein R2, R3, R6, R7, R8, R11, R12, R13, A, B, and Z are as defined in Claim 1.

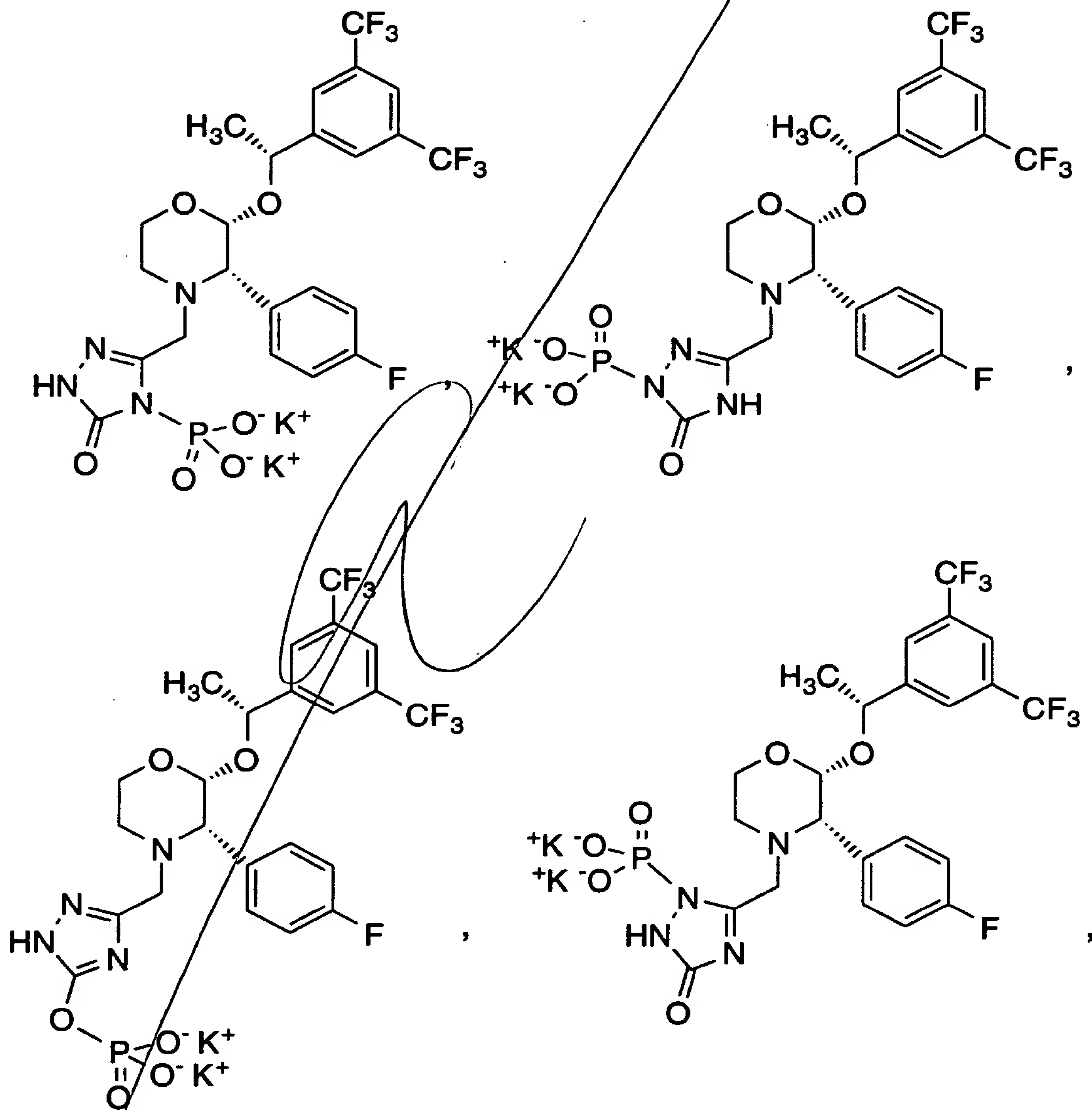
11. A compound which is selected from the group consisting of:

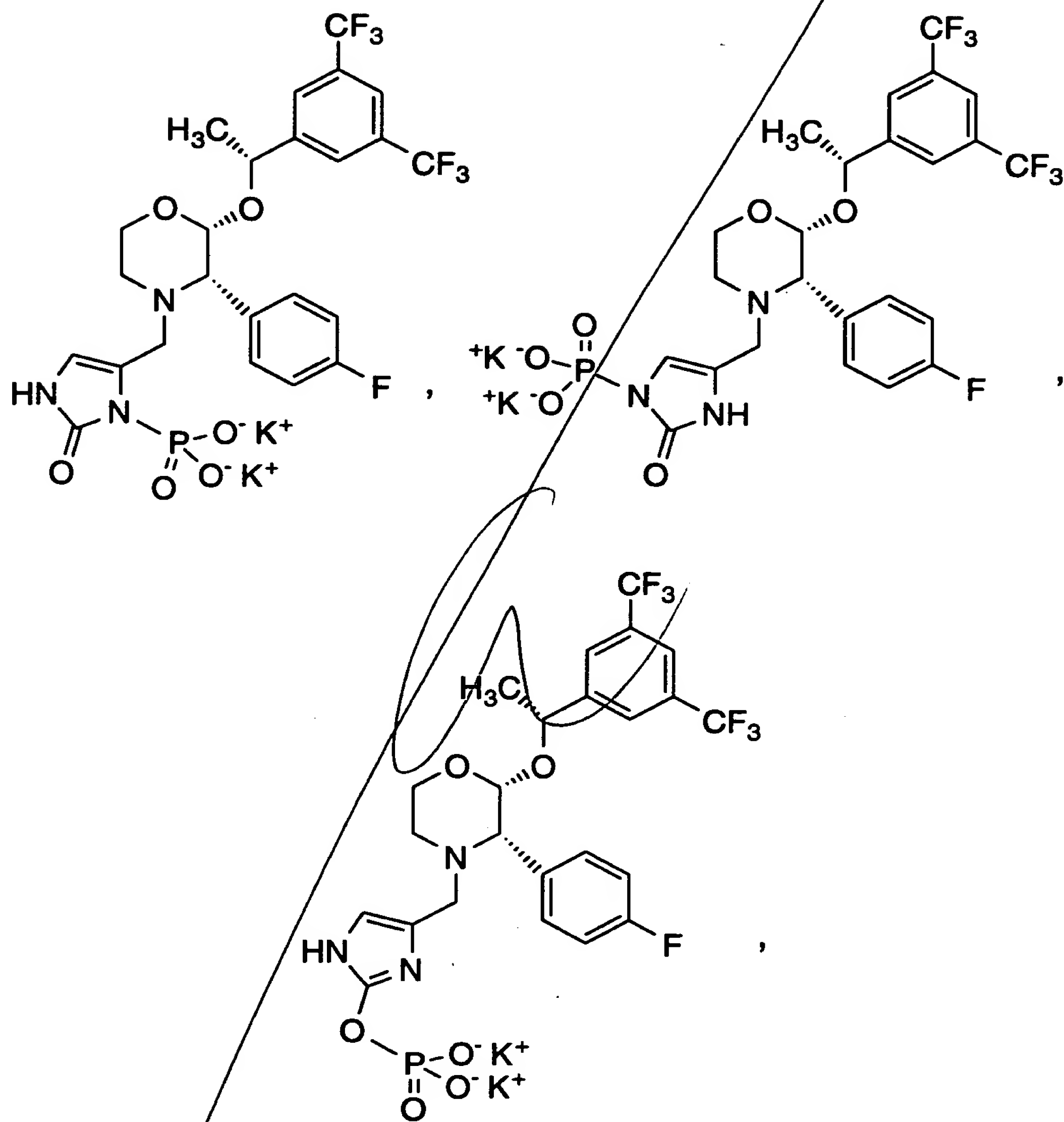
- 5 (1) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine N-oxide;
- 10 (2) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)-phenyl-4-(3-(4-monophosphoryl-5-oxo-1H-1,2,4-triazolo)methyl)morpholine;
- (3) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)-phenyl-4-(3-(1-monophosphoryl-5-oxo-1H-1,2,4-triazolo)methyl)morpholine;
- 15 (4) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)-phenyl-4-(3-(2-monophosphoryl-5-oxo-1H-1,2,4-triazolo)methyl)morpholine;
- 20 (5) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)-phenyl-4-(3-(5-oxyphosphoryl-1H-1,2,4-triazolo)-methyl)morpholine;
- 25 (6) 2-(S)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)-phenyl-4-(3-(1-phosphoryl-5-oxo-4H-1,2,4-triazolo)methyl)morpholine;

or a pharmaceutically acceptable salt thereof.

- 30 12. The compound of Claim 11 wherein the pharmaceutically acceptable salt is the bis(N-methyl-D-glucamine) salt.

13. A compound which is selected from the group consisting of:





wherein K^+ is a pharmaceutically acceptable counterion.

14. A compound which is:

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-
3-(S)-(4-fluoro)phenyl-4-(3-(1-phosphoryl-5-oxo-
4H-1,2,4-triazolo)methylmorpholine;

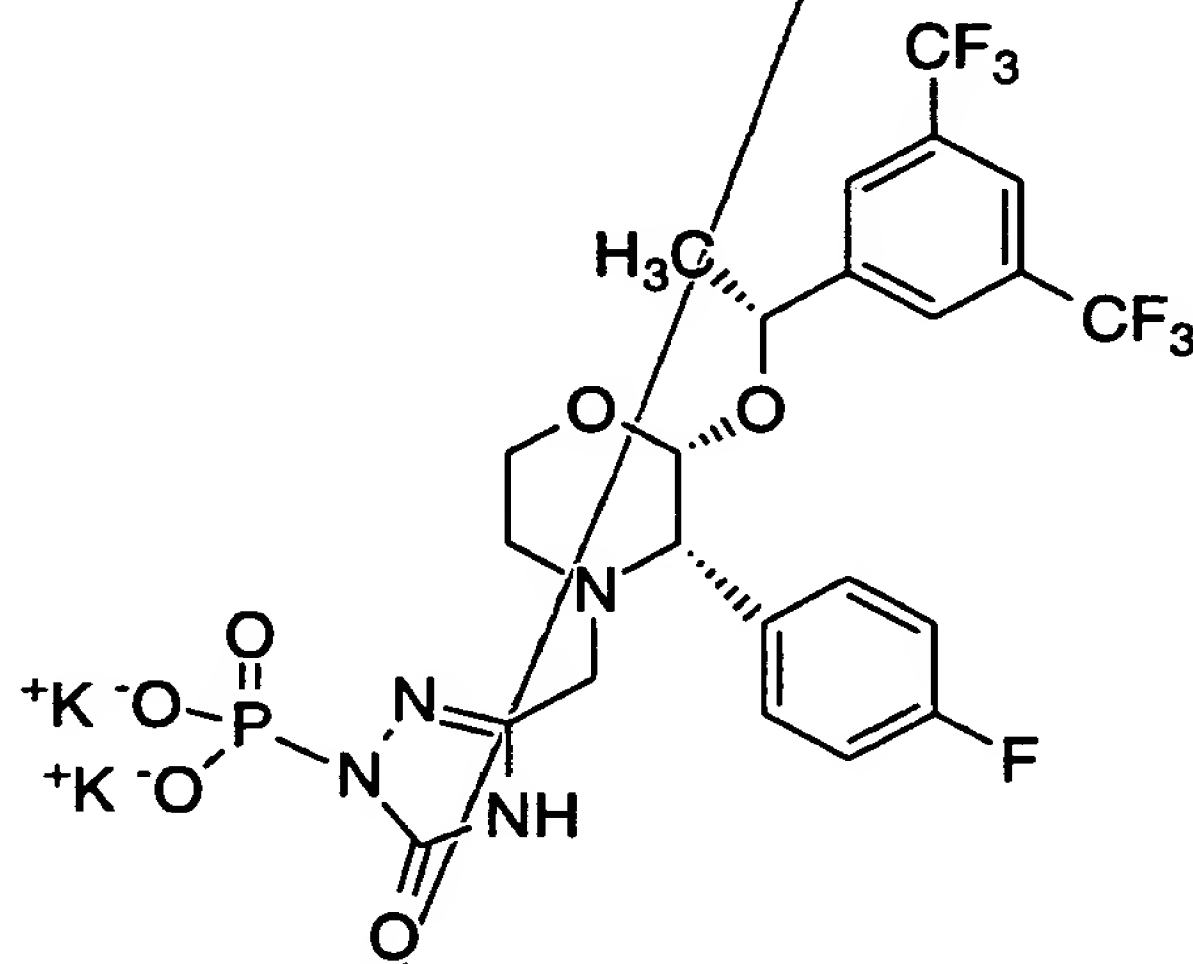
or a pharmaceutically acceptable salt thereof.

15. The compound of Claim 14 wherein the
pharmaceutically acceptable salt is the bis(N-methyl-D-glucamine) salt.

16. A compound which is

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-
(4-fluoro)phenyl-4-(3-(1-phosphoryl-5-oxo-4H-1,2,4-
triazolo)methylmorpholine, bis(N-methyl-D-glucamine).

17. A compound which is:

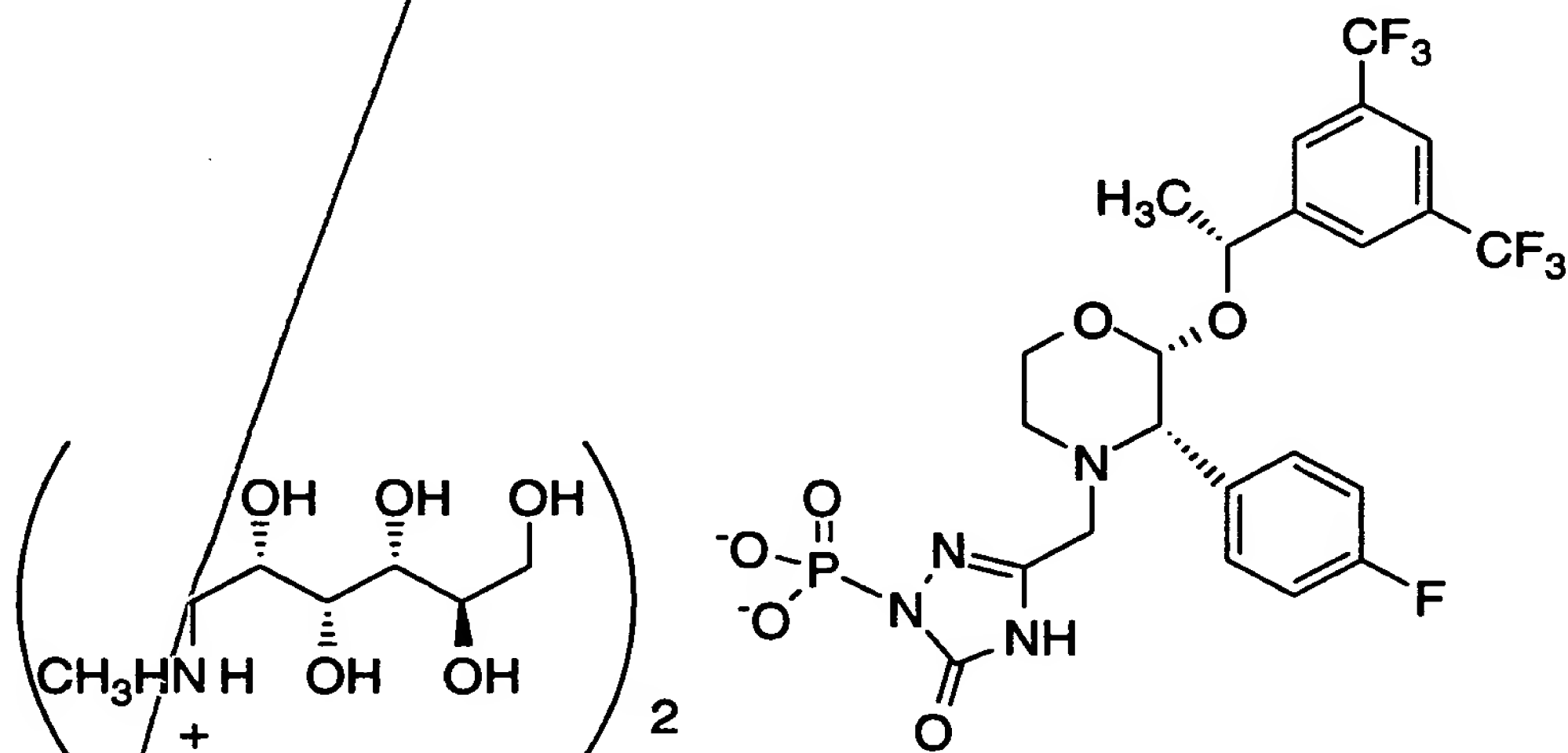


wherein K^+ is a pharmaceutically acceptable counterion.

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18. The compound of Claim 17 wherein K^+ is N-methyl-D-glucamine.

19. A compound which is:



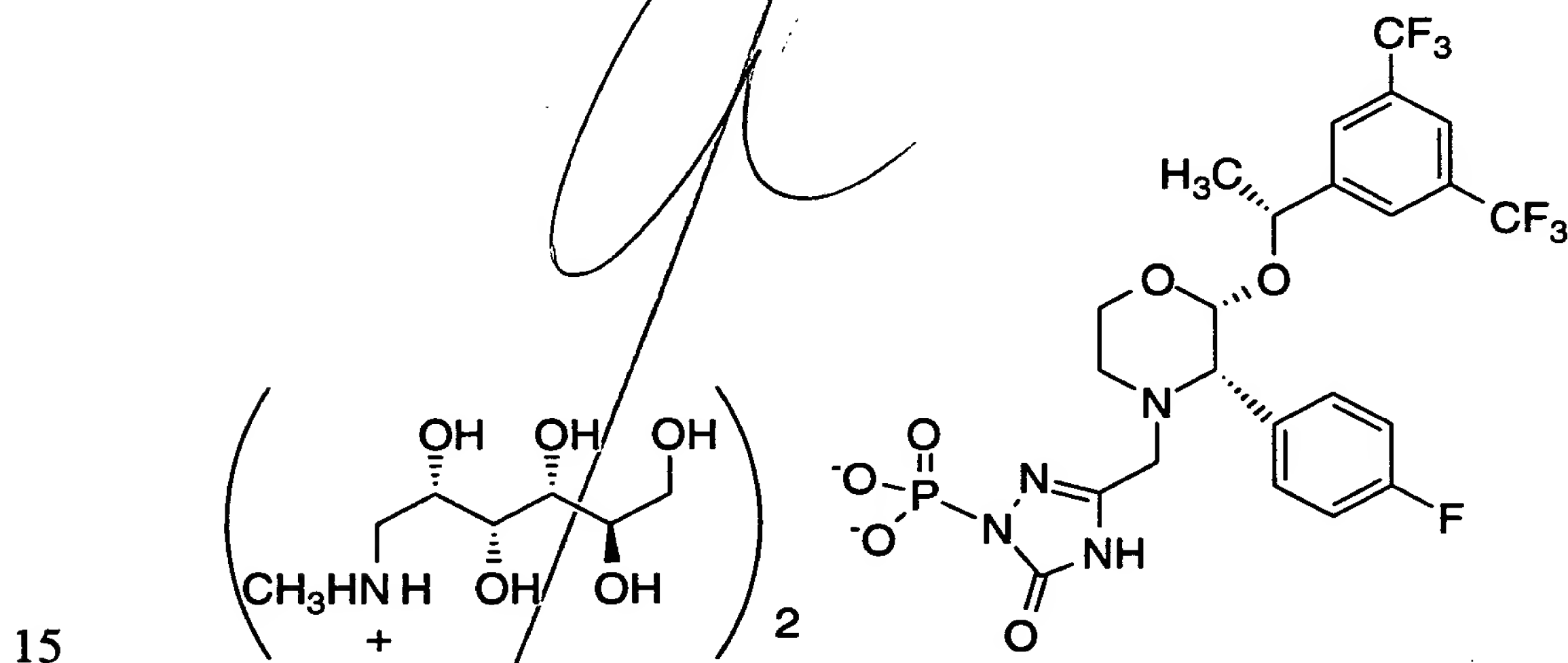
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20. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount of the compound of Claim 1.

5 21. The pharmaceutical composition of Claim 20 wherein the pharmaceutically acceptable carrier comprises water.

10 22. The pharmaceutical composition of Claim 20 wherein the pharmaceutically acceptable carrier comprises a physiologically acceptable saline solution.

23. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount of a compound which is:



20 24. A method for antagonizing the effect of substance P at its receptor site or for the blockade of neurokinin-1 receptors in a mammal which comprises the administration to the mammal of the compound of Claim 1 in an amount that is effective for antagonizing the effect of substance P at its receptor site in the mammal.

25. A method of treating or preventing pain or nociception attributable to or associated with migraine in a mammal in need thereof which comprises the administration to the mammal of an effective amount of the compound of Claim 1.

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26. A method of treating or preventing a condition selected from the group consisting of: diabetic neuropathy; peripheral neuropathy; AIDS related neuropathy; chemotherapy-induced neuropathy; and neuralgia, in a mammal in need thereof which comprises the administration to the mammal of an effective amount of the compound of Claim 1.

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27. A method for the treatment or prevention of asthma in a mammal in need thereof which comprises the administration to the mammal of an effective amount of the compound of Claim 1, either alone or in combination with a neurokinin-2 receptor antagonist or with a β 2-adrenergic receptor agonist.

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28. A method for the treatment of cystic fibrosis in a mammal in need thereof which comprises the administration to the mammal of an effective amount of the compound of Claim 1.

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29. A method for the treatment or prevention of emesis in a mammal in need thereof which comprises the administration to the mammal of an effective amount of the compound of Claim 1.

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30. A method for the treatment or prevention of arthritis in a mammal in need thereof which comprises the administration to the mammal of an effective amount of the compound of Claim 1.

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